

DESIGNING ARTIFICIAL RECEPTORS FOR THREAT AGENT DETECTION

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Abstract: Conformational searches were performed using molecular mechanics in the gas phase for monocyano-, regioisomers of dicyano-, tetracyano- and hexacyano- and octacyano-*meso*-octamethylcalix[4]pyrrole (**2**) to elucidate the factors responsible for conformational preference. The cyano function has a polarity quite similar to that of the previously investigated carboxamido function, but since its linearity results in fewer conformational possibilities, the computational task as well as interpretation of the results was simplified. Of the components of the Amber* force field, electrostatic and van der Waals attractive forces were typically the most important contributors to the global minimum for the series of compounds investigated. Flattened cone global minima conformations were found when **2** was incompletely substituted. With octasubstitution, significant destabilization of the flattened cone conformation was found relative to the doubly flattened 1,2-alternate due in part to a significant increase in bending energy. This suggest that hydrogen bonding plays a

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major role in stabilization of the flattened cone conformation of the octacarboxamido compound.

Introduction

Calix[4]pyrroles are intriguing cyclic oligomers formed by the condensation of pyrrole with carbonyl compounds other than formaldehyde (which produces porphyrins upon facile oxidation of the initial product) under acidic conditions. They have been demonstrated to function as effective hosts for a variety of chemical species including anions.¹ Unlike their close relatives, the calix[4]arenes² that have hydroxyl groups attached to their lower (or narrow) rim, unsubstituted calix[4]pyrroles are incapable of intramolecular hydrogen bonding since hydrogen bond accepting groups are absent. Consequently, the cone conformation is not favored for calixpyrroles unless a complex is formed with a suitable hydrogen bond acceptor ion such as chloride.³

Calculations have recently⁴ been performed that suggested that substitution at the 3,4-positions of each pyrrole ring of calix[4]pyrrole by appropriate substituents capable of intramolecular recognition was an effective means of stabilizing the cone with respect to other conformational possibilities (Figure 1.) Given the scope of the study and the fact that each molecule contained at least 68 atoms, a molecular mechanics solution to this problem was chosen instead of higher levels of theory. In addition, the molecular mechanics approach has the advantage that contributing energies (*vide infra*) to the total conformational energy are readily evident

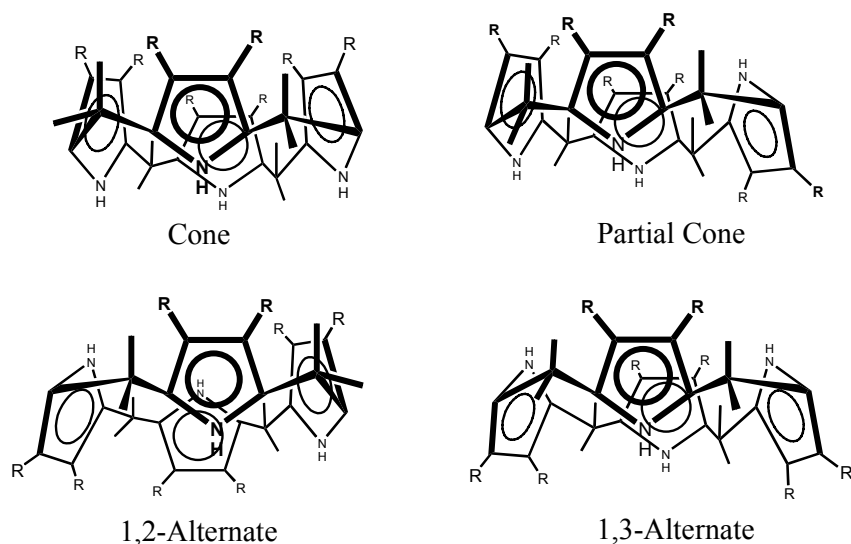
macroscopically in terms of familiar stereochemical and physical organic chemical treatments. It must be emphasized that molecular mechanics treatments are most effective when *relative* as opposed to absolute energies are calculated. Gas phase calculations were performed to assess intrinsic conformational preferences while avoiding complications introduced by surrounding solvent spheres or like molecules as in the crystal.⁵

Computational Methodology. Molecular mechanics calculations were carried out for the gas phase by means of Macromodel version 6.0 or 8.1⁷ using either an Octane, O2 or Indigo 2 Silicon Graphics workstation and the Amber* force field. This force field, although originally constructed for peptides has proven to be quite versatile⁸ was chosen in this instance because of its success with the related structurally related calix[4]arenes⁹ and its ability to closely reproduce the X-ray crystallographic structure of the octabromocalix[4]pyrrole, **I**, $R = \text{CH}_3$, $R^1 = \text{H}$, $R^2 = \text{Br}$. It is recognized that this comparison of these different phases, although extensively used in the literature to vindicate a computational method, is not unimpeachable; lattice forces, for example, are absent in the gas phase. The global minimum for each compound was identified by performing several conformational searches of at least 2000 steps starting from both the cone and the 1,3-alternate conformations using the Monte Carlo method until no new contributing conformations were identified. Each contributing conformation was separately minimized. Dipole moment calculations for model compounds were performed by means of AM1 semi-empirical calculations with Spartan, version 5.1.1.¹⁰

Results and Discussion

As was the case for the calixarenes,^{2,11} the cone conformation was determined to be flattened, with the calix[4]pyrrole backbone having C_{2v} as opposed to C_{4v} symmetry. For octasubstituted derivatives, three substituents, CONH_2 , CH_2OH and COOH were found to favor the cone conformation,⁴ in contrast to the unsubstituted compound which has a 1,3-alternate global minimum. This preference for the cone conformation is presumably due to the presence of intramolecular hydrogen bonding, and appropriate chain length such that hydrogen bonding in alternative conformations was unfavorable. A view from the top (wider rim) of the stable cone conformation of the octacarboxamido compound, **1**, in which the eight hydrogen bonds are drawn as dashed red lines is provided in Figure 2. Conformational searches demonstrated

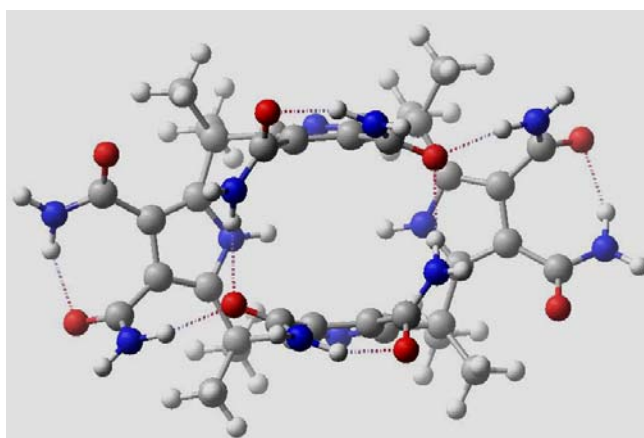
FIGURE 1. Conformers of Substituted meso-Octamethylcalix[4]pyrroles



that only the flattened cone conformation was populated over an energy range of at least 3.4 kcal/mol above the global minimum. While intramolecular hydrogen bonding was unquestionably a contributor to this stabilizing effect, it was of interest to identify additional factors that might be responsible for the overwhelming preference for these flattened cone conformations in the gas phase.

Conformational analysis of the octasubstituted compounds can be

FIGURE 2. View From Above the Stable Cone Conformation of the Octacarboxamido Derivative 1



facilitated by study of less substituted derivatives. Accordingly the monocarboxamido compound was selected for detailed study. It was somewhat surprising to discover that this compound, incapable of intramolecular hydrogen bonding, also had a flattened cone global minimum. A doubly flattened partial cone conformation, however, was found only 0.6 kcal/mol higher in energy, in addition to somewhat higher energy conformations. The total energies and descriptions of these conformations are presented in Table 1.^{11,12} If the reasonable assumption were made that entropy differences between these conformations were small, the flattened cone

conformation was responsible for only about 40% of the conformational distribution. Small changes in the free energy of a conformation can produce dramatic changes in conformational distributions; for example, that differ at room temperature by only 1.0 or 4.0 kcal/mole correspond to a mixture containing 85% and 99.9% of the more stable conformer, respectively.¹³ The energetically lowest seven conformers may be estimated to constitute 40, 20, 16, 10, 8, 4 and 2%, respectively. Also given in Table 1

TABLE 1. Contributing Energies (in kJ/mol) for the Important Conformations of the Monocarboamido Derivative

Conformation	a	b	c	d	e	f	g	h	i
Total Energy	-139.00	-136.54	-136.54	-134.91	-134.27	-132.14	-131.43	-123.37	-121.57
Stretching	3.24	3.25	3.68	3.38	3.39	3.41	3.65	3.60	3.86
Bending	93.03	91.58	93.11	92.11	94.71	91.75	92.24	92.84	93.16
Torsional	55.00	54.82	64.58	49.49	51.10	47.46	66.46	52.78	51.02
Improper Torsion	1.53	1.37	2.41	1.81	2.53	1.18	2.82	1.02	0.85
van der Waals	-32.48	-28.90	-28.62	-30.73	-34.03	-25.53	-26.12	-22.40	-18.77
Electrostatic	-259.31	-258.67	-271.23	-250.97	-251.97	-250.40	-270.47	-251.22	-251.70

- a. Flattened cone.
- b. Doubly flattened partial cone.
- c. Singly flattened partial cone.
- d. Doubly flattened partial cone.
- e. Flattened cone, two cyano groups on flattened pyrroles.
- f. Doubly flattened 1,2, two cyano groups on vertical pyrroles.
- g. Singly flattened 1,2-alternate, two cyano groups on flattened pyrroles.
- h. Severely flattened 1,2-alternate, two cyano groups on vertical pyrroles.
- i. Doubly flattened 1,2-alternate.

are the energies contributing to the total energy of each conformation. As expected, since bonds are difficult to stretch or compress,¹⁴ the stretching energies were found

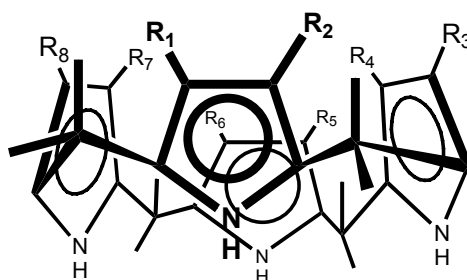
to make minor contributions to the total energy. The flattened cone owed its rather small relative stability to a subtle interplay of electrostatic and van der Waals contributions, as well as bending and torsional energies.

Given the complexities introduced by rotational isomerism about the bond connecting the carboxamido functionality to the pyrrole ring, it was decided to simplify the investigation by replacement with the linear cyano function, a group of similar polarity as established by AM1 calculations.¹⁰ Since the extensively hydrogen bonded network observed for the octacarboxamido compound (Figure 2), is impossible for the cyano analog; comparison of the structures provided insights into the additional factors contributing to the total energy of the cone conformation of **1**.

The results of the conformational searches for the monocyano derivative are provided in Table 2. As anticipated, the number of contributing conformations decreased considerably. Using the above assumption, the percentages of each contributing conformation were estimated. Clearly no overwhelming preference for any one conformation emerged; the flattened cone was favored due presumably to more favorable van der Waals interactions as the result of favorable dispersion¹⁵ of the electron clouds in the aromatic rings which were all oriented in the same general direction (Figure 1.)

Three dicyano derivatives were selected for study that were substituted either on the same or opposing rings. The contributing energies for the lowest energy conformations to the regioisomer, **2a**, $R_1 = R_2 = \text{CN}$, are provided in Table 3. It will be noted that the flattened cone conformation was calculated to be the global

minimum, 1.7 kcal/mol more stable than the next lowest conformation, the doubly flattened partial



2

TABLE 2. Conformational Energies for the Monocyano Derivative (in kJ/mol)

Conformation	a	b	c	d
Total	-48.78	-46.00	-43.30	-38.24
Stretch	2.40	2.56	2.65	2.79
Bending	86.43	84.94	84.85	85.88
Torsion	48.42	46.99	46.70	44.92
Improper Torsion	1.74	1.14	0.72	0.09
van der Waals	-29.19	-23.79	-21.81	-19.94
Electrostatic	-158.58	-157.84	-156.41	-151.98
Estimated Percentage	68	22	9	1

- a. Flattened cone.
- b. Singly flattened 1,2; CN on vertical pyrrole.
- c. Doubly flattened PC; CN on opp fl pyrrole.
- d. Twisted 1,3.

cone. The major contributor to relative stabilization of the flattened cone conformation was the van der Waals energy, consistent with the rationale for stabilization of the monocyano compound in terms of the relative positions of the pyrrole rings. Since the van der Waals contribution was of major importance it was

not surprising that the partial cone conformation with three partially aligned pyrroles would be next lowest in energy.

Table 3. Conformational Energies for Dicyano Derivative 2a

Conformation	a	b	c	d	e	f
Total Energy	-76.78	-69.64	-65.09	-63.05	-60.66	-56.41
Stretching	2.66	2.85	3.51	3.03	2.96	3.06
Bending	92.64	90.7	94.52	89.93	91.85	98.18
Torsional	51.6	47.98	54.62	46.93	46.61	47.22
Improper Torsion	3.15	1.78	3.91	0.68	0.51	1.53
VDW	-40.83	-30.61	-34.91	-24.87	-23.13	-22.87
Electrostatic	-186.02	-182.33	-186.57	-178.8	-179.5	-183.55
Percentage	93	5	1	0	0	0

a. Flattened cone.

b. Doubly flattened partial cone.

c. Flattened partial cone.

d. Doubly flattened partial cone.

e. Doubly flattened 1,2-alternate; cyano groups on horizontal pyrroles.

f. Doubly flattened 1,2-alternate; cyano functions on vertical pyrroles.

Dicyano regioisomers **2b**, $R_1 = R_6 = \text{CN}$, and **2c**, $R_1 = R_5 = \text{CN}$, were also calculated to have flattened cone global minima; however, there were four conformations other than the cone for the former and seven for the latter located within 1.1 kcal/mol and 1.9 kcal/mol of the global minima, respectively. The contributing energies are provided in Table S2. In the case of **2b**, the flattened cone was calculated to be only 0.5 kcal/mol more stable than the doubly flattened 1,2-alternate; in both of these conformations the cyano groups were located on the vertical pyrrole rings. Stabilization of the flattened cone was conferred by its van der Waals energy (0.9 kcal/mol) and by its electrostatic energy (0.5 kcal/mol); however, bending energy increases the flattened cone energy by 0.9 kcal/mol. The global

minimum of **2c** also has a flattened cone conformation; computations show that its van der Waals and electrostatic energies are 2.9 and 0.9 kcal/mol, respectively, more stable than the next lowest energy conformation, the singly flattened 1,2-alternate. The global minimum was destabilized by 1.1 kcal/mol due to unfavorable torsional energy. Comparing the global minimum of **2b** with that of **2c**, it was reasonable that stabilization conferred by van der Waals forces should be larger for the latter. Dispersion of the aromatic cloud should be a more facile process when a “mirror image” position in the opposing ring is not occupied by a cyano functionality.¹⁶ Since the energy differences calculated here were not large, these rationalizations should be treated cautiously.

For the compounds investigated to this point, even though the conformational searches consistently found a flattened cone conformation to be the global minimum, there was no overwhelming preference for this conformation. In addition, no predominant energy contribution could be identified that produced this consistent, but small conformational preference.

Two tetracyano compounds were next investigated. For regioisomer **2d**, $R_1 = R_2 = R_5 = R_6 = \text{CN}$, in which the opposing rings were substituted, the global minimum was again determined to be a flattened cone (Table S3.) A doubly flattened partial cone, a doubly flattened 1,3-alternate conformation and a severely flattened partial cone were found within 1.40 kcal/mol of the lowest energy conformation flattened cone conformation. The increase in energy of the higher energy conformations was due primarily to electrostatic destabilization and to destabilization due to van der Waals energy since the polarizable atoms of the pyrrole rings were in

general further apart than in the cone conformation. Interestingly a conformation was found 3.35 kcal/mol above the global minimum that was also a flattened cone. It differed from the global minimum in that the cyano groups were found on the flattened pyrrole moieties. As can be gleaned from Table 4, the electrostatic energy contributions of these conformations were virtually identical. This was in accord with a simple classical model¹⁷ in which the electrostatic energy was determined using only the charges of the pyrrole hydrogens and their separation, calculated by means of the charges and distances derived from AM1 semi-empirical methodology.¹⁰ It was reasonable to expect van der Waals interactions of the polarized rings would be more effective for the substituted vertical pyrrole rings that approach a parallel orientation of the aromatic π clouds as opposed to the orientations of the neighboring rings that approach orthogonality in the higher energy cone conformer. While the flattened cone bearing cyano substituents on vertical pyrroles had greater torsional energy than the horizontal (0.8 kcal/mol), the latter conformation was destabilized because its shape required the incorporation of increased bending energy.

Since the 1,3-alternate conformation was found to be reasonably stable, it was intriguing that a 1,3-alternate conformation with the cyano functions on vertical pyrrole moieties was not located in the conformational searches (Table S3.) When this conformer was generated with the same skeletal geometry as the computed 1,3-alternate conformation, minimization resulted in conversion to the previously found flattened cone global minimum. Clearly this structure is not a minimum on the conformational energy continuum. When a current energy calculation was

performed, it was found to have a significantly increased energy (17.2 kcal/mol) with respect to the stable 1,3-alternate conformation. The major contributors to this destabilization were the van der Waals and electrostatic energies. The results for **2d** may be summarized by noting that all conformations with severely flattened cones, i.e., the high energy severely flattened cone and the two 1,3-alternate structures, will be destabilized in terms of the van der Waals energy since attractive interaction of the pyrrole rings is limited. In addition, the presence of severely flattened rings between vertical pyrroles did not lead to a more positive electrostatic energy unless the vertical pyrroles were substituted by cyano functionalities. In this case, the strongly polarized rings interact unfavorably with the NH bonds of the flattened rings.

When the regioisomeric tetracyano compound in which the cyano groups were contained in neighboring rings was studied, **2e**, $R_1 = R_2 = R_3 = R_4 = \text{CN}$, two conformations, the flattened cone and the doubly flattened partial cone were the main contributors with the former predominating (Table S4.) For this compound, both electrostatic and van der Waals energies were influential in determining the relative energy of the global minimum with respect to the next lowest energy conformer, the doubly flattened partial cone.

Comparison of the results for **2d** and **2e** (Tables S3 and S4) permitted assessment of the relative effects of substitution in a neighboring as opposed to a transannular ring. Each regioisomer had a flattened cone global minimum with the doubly flattened partial cone contributing conformations had virtually the same energy: the doubly flattened 1,3-alternate in which the cyano groups were located

on the flattened pyrroles, and the severely flattened partial cone. Regioisomer **2e** was essentially represented by only two conformations.

The preference of the cyano groups in the flattened 1,3-alternate conformation of **2d**, could elucidated by calculating the current energy of that conformation in which this skeletal geometry was retained but the cyano functions placed on

TABLE 4. Comparison of Two Flattened Cone Conformers of the Tetracyano Derivative 2d (Energies in kJ/mol)

Conformation	a	b
Total	-60.48	-46.48
Stretch	3.37	3.05
Bending	104.93	111.61
Torsion	50.16	46.91
Improper Torsion	3.15	0.46
VDW	-44.45	-30.16
Electrostatic	-177.64	-178.36

a) Flattened cone with cyano groups attached to the vertical pyrroles.

b) Flattened cone with cyano groups attached to the horizontal pyrroles.

the vertically oriented pyrrole moieties. This results in significant increases in energy for the van der Waals and electrostatic energies (6.6 and 7.3 kcal/mol, respectively.) This conformation was transformed, as expected, into the global minimum flattened cone upon minimization.

When a current energy was calculated for the doubly flattened 1,3-alternate conformation of **2e**, obtained using the geometry of that conformer of **2d**, it was discovered that the total energy of the conformation was 9.3 kcal/mole higher than the

global minimum. This large increase in energy was essentially due to significantly more positive van der Waals and electrostatic energies. This energy increase was not as large as the analogous case for **2d** suggesting that transannular interactions were somewhat more unfavorable for doubly substituted pyrroles in the 1,3-alternate conformation. Since a substituted pyrrole would be oriented in a manner approaching perpendicularly in the flattened 1,3-alternate conformations with respect to its neighboring rings, it was reasonable to conclude that transannular interactions would result in greater destabilization either from van der Waals or electrostatic interactions.

Two additional tetracyano regioisomers, **2f**, $R_1=R_3=R_5=R_7$ and **2g**, $R_2=R_3=R_6=R_7$ also had flattened cone global minima. They were found to be considerably less stable than **2d** and **2e** (Tables S8 and S9.) Each of these molecules has singly substituted pyrrole constituents. The reason for this destabilization relative to disubstituted pyrroles will be discussed later.

Only one hexacyano derivative **2h**, $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = \text{CN}$, was studied. The global minimum was a flattened cone conformation in which four cyano functions were found on the flattened pyrrole rings. This result appeared to be at odds with the determination for tetracyano derivative **2d** for which there was a preference of more than 3 kcal/mole for the conformer in which the cyano functions were located on the vertical pyrroles. Interestingly, the simple electrostatic treatment described above to obtain relative energies was in general agreement with our calculations. By increasing the distance between the vertical pyrrole rings relative to the tetracyano derivative, at the expense of decreasing the distance between the

horizontal pyrroles, this flattened cone conformation was able to achieve relative stabilization.

Octasubstitution resulted in the first example in this series of cyanocalix[4]pyrroles for which the global minimum was found to be a conformation other than the flattened cone (Table S6.) Even though the van der Waals energy of the doubly flattened 1,2-alternate conformation was higher than that of the flattened cone, the latter was less stable electrostatically and requires an input of more bending energy to achieve its shape. Given the similar polarities of the cyano and carboxamido functionalities, it may be presumed that the octacarboxamido derivative would also assume a doubly flattened 1,2-alternate conformation in the absence of intramolecular hydrogen bonding. Over thirty conformations were found⁴ for the octacarboxamido derivative within 4.0 kcal/mol of the global minimum, each having at least 6 intramolecular hydrogen bonds and virtually identical skeletal structures. Conformational differences were produced by rotations about the bonds between the skeleton and the carboxamido functions.

To this point only regioisomers have been compared. Additional insights can be gained by examining the total and contributing energies of comparable calix[4]pyrrole backbones after all cyano groups have been removed. It is an oversimplification to assume that the calix[4]pyrrole skeleton is invariant over this series of compounds. This fact can be appreciated by study of the data presented in Table 5 that was obtained by replacing each cyano group by a hydrogen in the lowest lying flattened cone conformation (the global minimum in all cases with the

exception of the octacyano derivative) and calculating the single point energy. It can readily be observed that relative to *minimized* structure **M**, all skeletons have

Table 5. Single Point Energies of Calix[4]pyrroles Flattened Cone Skeletons after Removal of the Cyano Groups Relative to the Minimized Flattened Cone (kJ/mol)

	M	mono	2a	2b	2c	2d	2e	2f	octa
Total	-69.25	-63.08	-54.40	-56.38	-54.09	-40.84	-41.96	-29.81	-23.56
Stretch	2.44	2.38	2.66	2.62	2.48	3.34	3.32	3.78	4.52
Bending	79.88	86.49	92.26	92.89	91.54	104.23	104.99	118.3	128.04
Torsion	46.57	48.57	52.14	48.33	52.36	51.10	53.04	53.41	49.63
Imp Torsion	0.83	1.59	2.49	1.61	2.78	2.55	2.17	1.69	1.35
van der Waals	-19.87	-22.84	-24.52	-22.31	-25.15	-22.99	-25.82	-27.31	-27.35
Electrostatic	-179.09	-179.28	-179.42	-179.51	-178.83	-179.08	-179.57	-179.68	-179.76

increased energies. The additional bending energy contributions were found to be important to varying degrees (1.6 to 11.5 kcal/mol), while torsional energies were of minor of importance, responsible for 0.4 kcal/mol for the skeleton derived from **2b** to 1.6 kcal/mol for **2f**. All skeletons had more stabilizing van der Waals contributions to the total energy than **M** (0.6 – 1.8 ; kcal/mol) than **M**. This was due to the fact that **M** was a severely flattened cone with its neighboring vertical and horizontal pyrrole rings approaching orthogonality, an orientation in which stabilizing dispersion forces were least effective. Finally, electrostatic forces were essentially constant over this series.

When the total energy alone was examined, it was discovered that the stability of the skeleton increased with increasing cyano substitution. This observation indicated that the calix[4]pyrrole backbone had to be modified with respect to the

minimized conformation by increases to various energy components to accommodate additional substitution. The agreement of the total energies of regioisomers was < 0.6 kcal/mol.

When the contributing energies to the global minima of the regioisomers of compounds of the same degree of substitution were compared (Table S 9), it is apparent that the most profound variation was found in the electrostatic energies. Those regioisomers having doubly substituted pyrroles had considerably lower electrostatic energies than those possessing mono substituted rings. An explanation based on interaction between adjacent or transannular rings was invalidated by the observation that the electrostatic energies for a given regioisomer were approximately equal regardless of conformation. If these effects were at work it would be expected, for example, that there would be differences between the cone with all pyrroles rings having their nitrogen atoms directed in the same direction with respect to a plane perpendicular to the major symmetry axis of the molecular skeleton and the 1,2-alternate in which the two neighboring pyrrole nitrogens point in one direction and two in the opposite direction. When the AM1 electrostatic charges were calculated for 3-cyano-2,5-di-*tert*-butylpyrrole and 3,4-dicyano-2,5-di-*tert*-butylpyrrole, partial negative charge accumulation was found on the ring carbon(s) attached to the cyano group (Figure S4.) Charges at the remaining positions for these structures are similar. The electrostatic energies of atoms that define the difference between and mono- and disubstituted constituent model compounds are provided in Table S10. While the dicyano compound had to overcome the repulsive energies of the partially positive cyano carbons, this was more than compensated for by attractive energies

resulting from their interactions with partially negatively charged nonbonded cyano nitrogens and ring carbons. Thus, those most stable regioisomers that have larger number of monosubstituted rings were invariably less stable due not to unfavorable interactions with other rings, but rather due to an innate electrostatic instability of the constituent pyrroles themselves.

CONCLUSIONS

All cyanocalix[4]pyrroles for which molecular mechanics calculations were performed in this study had flattened cone global minima¹³ with the exception of the octacyano derivative. Preference for the cone conformation was a function of both the extent of substitution and regioisomerism. Of the energies contributing to the total energy, van der Waals and electrostatic inputs were the most influential. In the octasubstituted compound, the electrostatic and bending requirements overcame the favorable van der Waals interactions of the flattened cone conformation and destabilized this conformation with respect to the doubly flattened 1,2-alternate conformation. This conformation was effective in minimizing transannular and neighboring ring repulsive electrostatic effects, without eliminating attractive dispersion forces between the pyrrole rings. Since the cyano group was a reasonable model for the carboxamido functionality in terms of polarity, one can deduce that the fact that the octacarboxamidocalix[4]pyrrole existed exclusively in flattened cone conformations was due to the fact that hydrogen bonding can overcome the

destabilizing electrostatic, bending energies and van der Waal forces inherent in this conformation.¹⁹

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5. Of course, a knowledge of conformational preferences in solution and in the crystal are of considerable importance as these are the results that can most readily be applied to experiment; most often NMR studies and X-ray crystallography are applied, respectively. Reliable methods for determination of structures in certain solvents are the subject of an excellent review.⁶
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11. The terminology flattened cone which was established in the calix[4]arene literature will be used here indicating that two opposed pyrrole rings have been flattened. For the three major remaining conformations, specification of the number and location of the flattened pyrroles was necessary for an unambiguous description.
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18. From the point of view of attractive synthetic targets, these partially substituted global minima would be expected to be contaminated with varying degrees of additional diverse conformations. Furthermore, synthesis of partially substituted derivatives would present potentially daunting regioisomeric hurdles that would have to be overcome.
19. The carboxamido function is sterically larger than the cyano group.²⁰ The octamethyl derivative, substituted with groups more comparable in size prefers the “H” conformation.⁴
20. Reference 14b, p. 697. A values derived from cyclohexane derivatives are typically used to assess steric interactions. These values for CN, COOCH₃ (a

substitute for the unknown CONH_2) and CH_3 are 0.2, 1.2 and 1.7 kcal/mol, respectively.

